DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

P970026

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Yadin Kaufman
Myriad Ultrasound, Inc.
87 Walnut Court
Englewood, NJ 07631

MAY 29 1998

Re: P970026
SoundScan 2000 and SoundScan Compact
Filed: July 1, 1997
Amended: September 29 and October 24, 1997, and April 27 and May 15 and 29, 1998

Dear Mr. Kaufman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the SoundScan Sonometer. The intended use of the SoundScan Clinical Bone Sonometer is to:

> Perform quantitative ultrasound measurement of tibia (shin bone), the results of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone strength and, ultimately, in the determination of fracture risk.
>
> The SoundScan measures the velocity of ultrasound (speed of sound, SOS, in m/sec) along the tibia, exclusively within bone, unaffected by overlying soft tissue. SOS along the tibia provides an index of bone strength, with stronger bone having higher velocities. As such the SoundScan provides a measure of skeletal fragility. The SoundScan reports SOS along with both T-and Z-scores.

We are pleased to inform you that the PMA is approved subject to the condition described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section ~~520(e)~~ under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ewa Czerska at (301) 594-1212.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

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Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at

800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name:	Ultrasound bone sonometer
Device trade names:	SoundScan, Models 2000 & Compact
Applicant:	Mr. Yadin Kaufman Myriad Ultrasound Systems, Inc. 87 Walnut Court Englewood, NJ 07631
Premarket Approval Application (PMA) number:	P970026
Date of Panel Recommendation:	November 17, 1997
Date of Notice of Approval of Application:	May 29, 1998

II. INDICATIONS FOR USE

The intended use of the SoundScan Bone Sonometer is to perform quantitative ultrasound measurement of the tibia (shin bone), the result of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone strength and, ultimately, in the determination of fracture risk.

The SoundScan measures the velocity of ultrasound (speed of sound, SOS, in m/sec) along the tibia, exclusively within bone, unaffected by overlying soft tissue. SOS along the tibia provides an index of bone strength, with stronger bone having higher velocities. As such the SoundScan provides a measure of skeletal fragility. The SoundScan reports SOS along with both T- and Z-scores.

III. CONTRAINDICATIONS

None known.

IV. WARNINGS AND PRECAUTIONS

Warnings:

Prior to using the SoundScan, users should read the "Individualization of Treatment" item in the Essential Prescribing Information section in order to properly interpret patient results.

The SoundScan should not be used to assess patients whose skin is abraded and/or have an open sore in the area that comes into contact with the system.

The SoundScan should not be used in the presence of explosive agents.

Precautions:

Do not expose this instrument to rain or moisture.

For the SoundScan Compact, interfacing equipment (computer, monitor, printer) must meet IEC 601, or IEC 950 or equivalent safety standards, depending upon installation configuration. Refer to the SoundScan Installation Guide supplied with your system.

V. DEVICE DESCRIPTION

The SoundScan is a PC-based device which measures the velocity of ultrasound (speed of sound, SOS, in m/sec) along the tibia (tibial SOS), exclusively within bone, unaffected by overlying soft tissue. The device calculates the actual SOS along a defined longitudinal distance in the cortical layer of the tibia. Results are expressed in meters per second (m/sec), and are also presented in units of standard deviations relative to population reference values, e.g., statistical "T" (young-adult) and "Z" (age-matched) scores. Together with the complete history of patient measurements, results are displayed graphically and numerically, both on-screen and in printed reports. The device also includes a detailed patient file with complete biographic information and a profile of risk factors commonly associated with bone disease. Use of this file is at the discretion of the physician, and sections or all of it can be printed out as part of a comprehensive patient report. The patient file also provides automatic follow-up visit scheduling and tracking.

There are two models of the SoundScan; the 2000 and the Compact. The SoundScan 2000 is supplied as a complete mobile workstation, including an integral PC, printer, and console. The SoundScan Compact is a small, light and portable system component, and connects to a personal computer or laptop. (The computer must meet the minimum PC/laptop hardware requirements specified in the product specifications.) The difference between the two models is simply that the PC is integral to the SoundScan 2000, but external to the SoundScan Compact. Both models plug into a standard power outlet. Both models use the same ultrasound transducer and daily verification (QC) phantom, and share the same clinical measurement protocol, man-machine interface (user's interface), population reference values, and patient report format.

A) DEVICE COMPONENTS

The SoundScan consists of three major components: the ultrasound transducer, the electronic unit, and the verification phantom.

The ultrasound transducer is the element which actually sends and receives acoustic signals to and from the patient's body. The watertight transducer is a single unit, and houses all ultrasound components.

The electronic unit contains all the SoundScan hardware, including the proprietary analog and digital circuitry and a medical grade isolation power supply. The electronic unit for the SoundScan 2000 incorporates an integral PC. The electronic unit for the SoundScan Compact incorporates the communication circuitry necessary to communicate with an external computer.

The verification phantom is provided for daily system verification (QC). The phantom simulates human bone and has known, stable characteristics.

Peripheral equipment for the SoundScan 2000 includes monitor, keyboard, mouse, printer, mobile console, and a footswitch for hands-free, on/off control of the measurement. Peripheral equipment for the SoundScan Compact includes a communication adapter for connection to the computer and printer, and a footswitch.

The SoundScan is supplied with both an Installation Guide and a complete User's Guide which includes physician and patient educational material, and the SoundScan Patient Questionnaire, a data collection form which mirrors the system's patient file. Accessories include a tape measure and skin marker for determining the measurement site, and commercially available ultrasound gel.

B) DEVICE OPERATION

SoundScan measurements are made across the tibial plane at the mid-tibia with the patient sitting or lying down. The mid-tibia is defined as the midpoint between the apex of the medial malleolus and the distal apex of the patella, identified by palpation with the patient's leg in the extended position. A complete patient measurement consists of a series of SOS readings (samples) taken as the transducer is moved across the tibial plane, along the mid-tibial circumference. At the conclusion of the 2-3 minute measurement, a single representative result is automatically computed and displayed. Standard commercial ultrasound gel is applied to the region to facilitate acoustic contact.

No instrument calibration is required. Daily system verification is performed using the verification (QC) phantom supplied with the device. The SoundScan provides PASS/FAIL feedback to the operator. For long-term stability confirmation, the device both displays and prints trends of the phantom measurements over time, and outputs this data as a spreadsheet-compatible file.

C) PRINCIPLES OF OPERATION

Once the transducer is positioned correctly over the bone, a proprietary geometric array of ultrasonic piezo-elements ignores the overlying soft tissue, and thus measures SOS only in the bone. Using feedback from the transducer, the system provides on-screen cues to guide the operator to achieve correct positioning. The system automatically measures the time required for an ultrasound wave to propagate a defined distance along the tibial cortex. Actual SOS within bone is then calculated as this distance divided by the measured time. SOS provides an index of bone strength, with stronger bone having higher values.

VI. ALTERNATE PRACTICES / PROCEDURES

A) BONE DENSITOMETRY (BMD)

Over the past twenty years, bone densitometry has established itself as a useful tool for skeletal assessment. Densitometry, by measuring the attenuation of an x-ray or gamma ray beam through a bone, is used to assess the direct impact of skeletal diseases such as primary and secondary osteoporosis and Paget's disease, and the indirect consequences of conditions such as chronic renal failure.

Densitometry techniques use ionizing radiation, and focus on either area or volumetric measurements of bone mineral density (BMD). Methods of measurement include single and dual gamma photon absorptiometry with radionuclide sources (SPA and DPA), single and dual x-ray absorptiometry with x-ray tube sources (SXA and DEXA), and spinal and peripheral quantitative x-ray computed tomography (QCT and pQCT) [2]. Densitometry provides an estimation of BMD both on an absolute scale, and also relative to population reference values. As such, it provides additional information on which to base diagnostic and therapeutic decisions.

B) QUANTITATIVE ULTRASOUND (QUS)

Quantitative ultrasound (QUS) is an alternative method for skeletal assessment. It has been demonstrated that QUS can discriminate effectively between patients with hip fractures and healthy individuals [7], and can predict hip fractures similarly to densitometric techniques [8].

C) BIOCHEMICAL BONE MARKERS

Bone markers are an indirect measurement of the rate of bone resorption and/or bone formation, and are intended to identify people who have higher levels of bone resorption enzymes or proteins. Bone markers do not provide an absolute baseline skeletal assessment; rather a measure of rate-of-change.

Therefor people with the lowest present bone quality and/or the highest rate of bone loss are considered to be the highest risk for future fractures.

VII. MARKETING HISTORY

The SoundScan is currently marketed in over 30 countries worldwide, including Europe, Latin America, Asia, and the Middle East. Neither SoundScan model has been recalled or withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

There are no known potential adverse effects of this device on health. Of the 5,357 people assessed during the clinical evaluation program, there were no reported complications, adverse events or side effects. No adverse events have been reported from systems installed internationally.

IX. SUMMARY OF PRECLINICAL STUDIES

A) ACCURACY

In-vitro (phantom) accuracy was assessed following the FDA Draft Guidance for Review of Bone Densitometer 510(k) Submissions (9-Nov-92, CDRH). To access accuracy, measurements were made of the absolute difference between the mean obtained with the device and the correct (i.e. reference) value of the object under test, divided by the correct value, and expressed as percent.

An epoxy-glass plate was used as the object-under-test because its SOS characteristics are similar to those of human bone. The SoundScan measurement of SOS in this plate was compared to that measured using a dedicated bench-top test fixture, which was defined to be the standard for these experiments. SoundScan SOS values were found to agree closely, i.e. to within 2 m/sec, with the reference test fixture, demonstrating a percentage difference of 0.05%.

In addition, comparison of the SoundScan method of longitudinal transmission to two independent techniques (through-transmission and echo-mode) was also made. Though different ultrasound measurement methods are known to differ somewhat in their results, SOS measurements with the SoundScan were in close agreement with those obtained by the other techniques, i.e. to within 4 m/sec, demonstrating a percentage difference of 0.15%.

Thus accuracy was high, as expressed by a range of percentage differences from 0.05% to 0.15% in three different experimental methods, which is within stated product specifications.

B. REPRODUCIBILITY

In-vitro (phantom) reproducibility, as expressed by precision error, was assessed following the FDA Draft Guidance for Review of Bone Densitometer 510(k) Submissions (9-Nov-92, CDRH). Precision error was defined as the standard deviation of repeated measurements made by one operator on one phantom, divided by the mean of the measurements, and expressed as percent. Repeated results were obtained during several formal evaluations.

Precision error ranged from 0.03% to 0.1%, and is within stated product specifications.

C. SOFT TISSUE ERROR

The purpose of this study was to demonstrate that SoundScan in-vivo tibial SOS measurements are not influenced by either the presence or the properties of the overlying soft tissue.

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Epoxy-glass and machined bovine bone substrates were used to simulate human tibia because their velocity characteristics span the typical human tibial range. Results obtained through direct measurements on the substrates were defined to be the reference for all subsequent experiments. Chicken breast, at different states of preservation, was placed over the substrate to imitate soft tissue, and measurements were repeated.

The accuracy of all measurements, regardless of substrate or state of preservation of the soft tissue used, was high, with a percentage difference of <0.1%, which is within stated product specifications.

D. SENSITIVITY TO CORTICAL THICKNESS

It is known that aging and certain bone diseases such as osteoporosis are accompanied by thinning and increased porosity of the cortical layer of bone. It has also been observed that these changes coincide with a reduction in tibial SOS. The objective of this study was to assess the sensitivity of the SoundScan to cortical thickness. The unique feature of measuring longitudinal transmission enables quantification of such a parameter. The relationship between sound velocity and thickness was analyzed for 3 different types of materials (Perspecs, bovine cortical bone, and fiberglass).

Results show a direct relationship between thickness and measured SOS. For the three materials, SOS decreased by tens of m/sec per mm reduction in thickness.

E. EX-VIVO BIOMECHANICAL TESTING: TIBIAL SOS AND TIBIAL BMD VERSUS TIBIAL STRENGTH

This in-situ study was designed to verify that SoundScan measurements correlate with the mechanical properties of human, tibial cortical bone, and to compare tibial SOS with tibial BMD.

Twenty-six human cadaver lower limbs were used (mean age 81+/-12 years, age range 53-98 years). After assessing the longitudinal tibial SOS of the intact limbs using the SoundScan device, a cylindrical sample of cortical bone was removed from the anterior tibia of each limb, and its density (gm/cm^3) was determined using peripheral quantitative computer tomography (pQCT). The same specimen was then mechanically tested in tension to failure. Eleven specimens had valid mechanical test results.

Both log-transformed tibial SOS and density correlated strongly with log-transformed elastic modulus, yield strength, and ultimate strength of tibial cortical bone ($0.87 \leq r \leq 0.98$, $p<0.0001$). In addition, the elastic modulus (E) was calculated using measured tibial SOS and BMD values, according to the relationship $\mathbf{E} = \rho v^2$, where ρ was the pQCT density result, and v the tibial SOS result. Strong correlations were found between the calculated E and the measured values of E ($r=0.97$, $p<0.0001$), ultimate strength ($r=0.92$, $p<0.0001$), and yield strength ($r=0.92$, $p<0.0001$). Finally, tibial SOS correlated strongly with tibial BMD ($r=0.86$, $p<0.0001$).

The results demonstrate that tibial SOS reflects mechanical parameters of bone. Furthermore, tibial SOS correlates strongly with tibial BMD for mechanical assessment of bone.

F. BIOCOMPATIBILITY

The natural rubber cover on the bottom of the transducer is the only material which comes in contact with the patient. Cytotoxicity, primary skin irritation, and dermal sensitization testing was conducted following good laboratory practices (GLP) and using standard accepted protocols. Dermal sensitization testing was performed with both polar and non-polar solvents. Although considered cytotoxic, the material caused no adverse reactions in the irritation and sensitization tests.

G. PHYSICS

Myriad Ultrasound Systems submitted test data on six piezo-ceramic transmitters (3 high frequency transceivers and 3 low frequency transmitters). The measurements were made in adherence to NEMA UD2-1992 (Acoustic Output Measurement Standard for Diagnostic Ultrasound Equipment) and FDA 510(k) Guide for Measuring and Reporting Acoustic Output of Diagnostic Ultrasound Medical Devices (April, 1995). The results form the basis for the Ultrasound Output (nominal) product specifications listed below (among others), and are well within the limits specified in the CDRH Guidance "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" issued on September 30, 1997.

Mechanical Index ***MI***	0.25 MHz: < 0.6 1.00 MHz: < 0.3
Derated spatial-peak, pulse-average intensity $I_{sppa.3}$	0.25 MHz: < 1.0 W/cm^2 1.00 MHz: < 1.5 W/cm^2
Derated spatial-peak, temporal average intensity $I_{spta.3}$	0.25 MHz: < 3.0 mW/cm^2 1.00 MHz: < 3.0 mW/cm^2
Ultrasound power W_o	0.25 MHz: < 7.0 mW 1.00 MHz: < 4.0 mW

H. ELECTROMAGNETIC COMPATIBILITY

Myriad Ultrasound Systems verified compliance of both SoundScan models with the requirements of EMC Directive 89/336/EEC as amended by 92/31/EEC and 93/68/EEC. The devices were tested according to the requirements of EN60601-1-2 and the associated IEC 801-2:1991, IEC 801-3: 2nd edition, IEC 801-4: 1988, IEC 801-5: 65A/77B (sec) 136/101, and EN55011 standards.

I. ELECTRICAL SAFETY

Myriad Ultrasound Systems verified compliance with the safety requirements of IEC 601-1:1988, IEC 601-1 A1:1991, IEC 601-1 A2:1995, and IEC/TC 62B/87/1993 (Draft) for the SoundScan 2000, and EN 60601-1/1990, A1/1993, A2/1995, and IEC/SC 62B/601-2-37 (Draft) for the SoundScan Compact. Both models are Class I with Applied part Type BF. The SoundScan Compact is classified as a component.

J. SOFTWARE

Software verification tests used to test the SoundScan software were submitted and found to be adequate. A hazard analysis indicated that all software and hardware patient and user concerns were adequately addressed. Verification, validation and unit testing demonstrated that the device will operate in a manner as described in the specifications.

K. SOUNDSCAN 2000 VERSUS SOUNDSCAN COMPACT

To demonstrate equivalence between the two SoundScan models, in-vitro (phantom) accuracy and reproducibility were assessed in a side-by-side comparison, performed as per the FDA Draft Guidance for Review of Bone Densitometer 510(k) Submissions (9-Nov-92, CDRH). A standard production verification phantom was used as the reference.

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Both SoundScan 2000 and SoundScan Compact SOS values were found to agree closely, i.e. to within 2 m/sec, with the reference value, demonstrating an accuracy of ≤0.06%. Reproducibility for both models was ≤0.03%.

The study demonstrates that both models demonstrate equivalent performance, and both performed within stated product specifications.

X. SUMMARY OF CLINICAL STUDIES

A) INTRODUCTION

Myriad Ultrasound performed clinical studies at six international sites in the U.S.A., Israel, United Kingdom, and Germany. The objective of the studies was to *demonstrate that tibial SOS is a useful clinical indicator of skeletal status, it is both necessary and sufficient to show that (1) it provides accurate and precise results, (2) it behaves in a similar manner to other accepted assessments of skeletal status, i.e. peripheral and axial BMD, relative to age, menopause and gender, and (3) it can discriminate between patients with and without low trauma fractures in a comparable way to other accepted assessments of skeletal status, i.e. peripheral and axial BMD.*

B) CLINICAL STUDIES

General

The objective of the studies was to verify expected performance trends of tibial SOS, and to compare its performance with today's state-of-the-art peripheral and axial densitometry, in order to confirm the above thesis. Accuracy of the SoundScan was assessed in in-vitro non-clinical studies. All other aspects of the thesis were evaluated by the six primary clinical studies.

All the studies were similar in design, although not identical. All studies were cross-sectional and retrospective, and recruited volunteers from hospital or clinic patients and/or staff, or through local advertising. In the key discriminatory analyses, vertebral fractures were diagnosed by accepted methods, i.e., x-ray assessment and/or patient history, and patient history for appendicular fracture.

Tibial SOS measurements were performed as per standard SoundScan instructions. Hip and spine BMD, and proximal forearm BMD of the radius were measured using single photon absorptiometry (SPA), single x-ray absorptiometry (SPX), or dual x-ray absorptiometry (DEXA). Each center followed a consistent protocol regarding measurement site. To represent actual clinical use, only one measurement was performed per patient for each technology (except for precision assessments, where repeat measurements were made).

The studies were designed to assess the following performance characteristics: in-vivo precision, the relationship of tibial SOS to anthropometric parameters, and comparison of tibial SOS to peripheral and axial BMD, with respect to their ability to discriminate between postmenopausal women with and without a history of low-trauma fractures (vertebral or appendicular).

1. In-vivo precision

Precision was assessed by repeat measurements on several subjects by one or more operators.

Precision was calculated as the coefficient of variation, as per the FDA Draft Guidance for Review of Bone Densitometer 510(k) Submissions (9-Nov-92, CDRH). Standardized precision, also referred to as the Standardized Coefficient of Variation (SCV) was calculated as per Miller et al.

[9]. SCV is a method for standardizing and comparing precision across different technologies, and provided for gross comparison between tibial SOS and peripheral and axial BMD.

In-vivo precision of the SoundScan measurement was calculated as the coefficient of variation based on repeated measurements on a set of individuals. Precision was determined in groups of 10 to 97 subjects at five of the clinical centers. A total of 492 measurements were performed on 192 subjects who ranged in age from 22 to 80 years. The subjects included healthy people, bone clinic patients, and patients with diagnosed osteoporosis. Results are summarized in Table 1, as compared to published results for axial and peripheral BMD. Also shown is the Standardized CV% (SCV), calculated using actual tibial SOS data, and published BMD precision data combined with actual population means and ranges taken from these PMA studies.

	SoundScan tibial SOS	**BMD (Spine, hip, forearm)**
Mean CV%	**0.37%**	1.0 - 3.0%*1
Standardized CV%*2	**3.1%**	1.5 - 5.2%

Table 1: In-vivo precision

*1 CV% for BMD is cited from ***Noninvasive Assessment of Bone Mineral and Structure: State of the Art***, Journal of Bone and Mineral Research (JBMR), 1996, H.Genant et al., Vol. 11 (6) 707-730 [2]

*2 Standardized CV% is defined in Miller et al. [9]. Standardized CV% was calculated for both the SoundScan and BMD, using the CV% cited above and population means and ranges derived from the data of 97 to 3023 women across the various centers.

2. The relationship of tibial SOS to anthropometric parameters, and comparison to peripheral and axial BMD

All study participants were measured with tibial SOS. BMD measurements were also made as specified in the individual study protocols. The relationships between tibial SOS and other technologies to anthropometric parameters (age, height, weight, body mass index, age-of-menopause, and years since menopause) were assessed by correlation. In addition, the annual linear increase/decrease of tibial SOS was determined as a function of age, derived as the coefficient in the linear regression of tibial SOS on age, expressed as meters/sec/year. For these analyses, p-values below 0.05 were considered statistically significant.

The correlation of SoundScan tibial SOS measurements with anthropometric parameters, i.e., age, years since menopause, height, weight, and BMI was determined for women at five clinical centers. Concurrent axial and peripheral BMD measurements were obtained where possible. Results are summarized in Table 2, which shows the range of correlation results. (Data from the sixth center is excluded because it is biased by intentional pre-selection and does not allow for valid comparison). Cohort sizes across the various centers ranged from 176 to 3023 women. (Results whose p-value ≥ 0.05 are non-significant, NS). Tibial SOS behaved similarly to BMD relative to anthropometric parameters, insofar as it exhibited expected reduction relative to age and menopause.

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	Range of values, r			
	Tibial SOS	**Hip BMD**	**Forearm BMD**	**Spine BMD**
Age	**-0.45 to -0.60**	-0.28 to -0.56	-0.55 to -0.65	-0.35 to -0.52
Years since MP	**-0.27 to -0.53**	NS to -0.45	-0.41 to -0.46	NS to -0.46
Height	**0.16 to 0.33**	NS to 0.44	0.31 to 0.42	0.27 to 0.41
Weight	**NS to 0.20**	0.26 to 0.40	0.18 to 0.31	0.28 to 0.40
BMI	**NS to -0.06**	NS to 0.42	NS to 0.19	NS to 0.31

Table 2: Correlation to anthropometric parameters for women

Linear trends of SoundScan tibial SOS versus age for Caucasian pre- and postmenopausal women are shown in Figure 1 for each of five of the clinical centers. SoundScan tibial SOS exhibits a statistically insignificant change in premenopausal adulthood, followed by a significant decrease in the postmenopausal years.

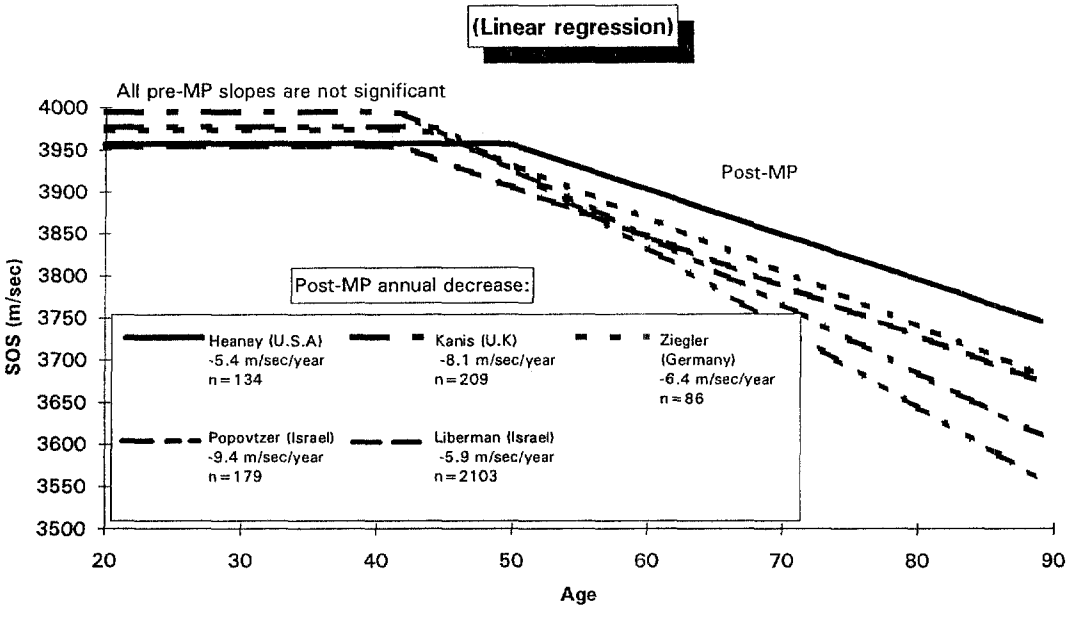

Figure 1: Tibial SOS versus age for Caucasian pre- and post-MP women

For the two clinical centers studying both women and men, Figure 2 shows the annual linear rates of change in tibial SOS for the entire population. Tibial SOS declines 2.5 to 3.4 times as fast per annum in Caucasian women as in men, based on studies comprising 371 and 3737 people (~ -4.7 m/sec/year for women, ~ -1.6 m/sec/year for men). For each sex, results from the two clinical centers were statistically significant.

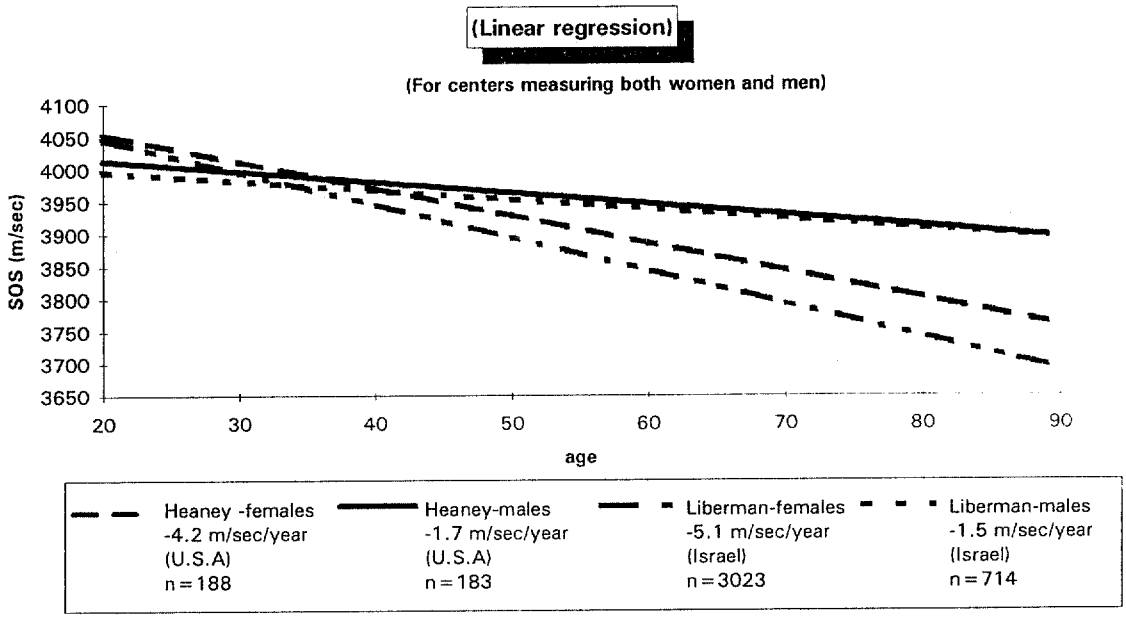

Figure 2: Annual linear rates of change of tibial SOS for Caucasian women versus men

3. Discriminatory ability of tibial SOS for postmenopausal women with appendicular and vertebral low trauma fractures, and comparison to peripheral and axial BMD. Comparison to both premenopausal and age-matched, non-fracture controls.

This set of analyses was deemed to be the most important part of the entire clinical studies program. As diagnosed using radiography and patient history, as specified in the individual protocols, patients with and without fracture were compared to evaluate the degree of separation of their tibial SOS measurement results. For comparison, peripheral and axial BMD were also assessed. For those centers with both tibial SOS and densitometry measurements, comparisons were performed using only matched data, i.e. only those subjects with a complete set of tibial SOS and densitometry measurements were analyzed. Appendicular fracture was defined to include any non-vertebral fracture, and includes hip, wrist, ankle etc.

For all women, the presence or absence of appendicular fracture was ascertained by patient history. The presence or absence of vertebral fracture was determined by x-ray in postmenopausal women. (In the population reference values study, vertebral fractures were diagnosed by patient history). Premenopausal women had no history of low trauma fracture, and were assumed not to have any low trauma vertebral fracture unless information to the contrary was made known to the clinician in the patient file or study questionnaire. Fracture/non-fracture discrimination was assessed by t-tests, ROC curves, areas under the ROC curves, sensitivity/specificity, and odds ratio analyses. As relevant, p-values below 0.05 were considered statistically significant. Where measurements were performed with more than one technology (e.g. tibial SOS, spine, hip, and forearm BMD), the cohorts were "matched", i.e. each subject had measurements with all technologies.

Discriminatory ability was defined as the ability of the SoundScan to discriminate between postmenopausal women (Post-MP) with low trauma fractures and two groups; premenopausal (Pre-MP) and postmenopausal non-fracture controls. This was studied in a total of 2057 women at six centers, including 1201 age-matched comparisons, as shown in Table 3. Totals at the individual centers ranged from 63 to 1206 women each.

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Pre-MP non-fracture	856
Post-MP non-fracture	814
Post-MP fracture (162 appendicular fx, 225 vertebral fx)	387
Total	2057

Table 3: Discriminatory analysis: # women

SoundScan tibial SOS demonstrated significant discriminatory ability, similar to BMD, for postmenopausal low trauma appendicular and vertebral fractures versus premenopausal non-fracture controls (5 centers). Sensitivities of tibial SOS (at T=-1SD) ranged from 83% to 100% for appendicular fracture and 64% to 93% for vertebral fracture. Associated specificities ranged from 84% to 89% for both types of fractures. Hip, forearm, and spine BMD results were similar. To lend clinical perspective, mean T-scores were calculated for the fracture cohort relative to the individual center's non-fracture control group. Results are shown in Table 4.

Fracture type	**#centers**	**n, total**	**Mean T-score (Range)**
Appendicular fracture	3	162 fx, 758 non-fx	**-3.4** (-2.3 - -4.6)
Vertebral fracture	4	121 fx, 815 non-fx	**-2.4** (-1.6 - -3.1)
Overall average, both types	5	283 fx, 856 non-fx	**-2.8**

Table 4: Mean T-scores for fracture cohorts

SoundScan tibial SOS demonstrated significant discriminatory ability for appendicular, low trauma fractures versus age-matched, non-fracture controls, as determined by t-tests for differences between the means (3 centers).

Three centers reported significant discriminatory ability of SoundScan tibial SOS for postmenopausal low trauma, vertebral fractures versus age-matched, non-fracture controls as determined by t-tests for differences between the means. Two centers found non-significant discrimination. In the latter two studies, hip and forearm BMD also did not reveal any significant difference between the fracture and non-fracture cohorts. Associated odds ratios ranged from non-significant to 2.5, and behaved similarly for hip, forearm, and spine BMD.

Receiver operating characteristic (ROC) curve analysis revealed areas under the curves (AUC) as shown in Table 5. Results whose p-value ≥ 0.05 have an area which is not significantly different from 50%, and are listed as NS.

Populations compared	Range of ROC AUC results for various diagnostic modalities			
	SoundScan tibial SOS	**Hip BMD**	**Forearm BMD**	**Spine BMD**
Post-MP appendicular fx versus pre-MP non-fx	93%-98%	Not studied	93%	Not studied
Post-MP vertebral fx versus pre-MP non-fx	84%-95%	84%-94%	84%-90%	93%
Post-MP appendicular fx versus age-matched non-fx	NS-78%	Not studied	NS	Not studied
Post-MP vertebral fx versus age-matched non-fx	NS-75%	NS-66%	NS-69%	NS-71%

Table 5: Areas under the ROC curves

4. Population reference values for women and men

Reference values were built for clinical use, to allow comparison of patients to healthy reference values for assessment of bone. The primary target was Caucasian women, the population most associated with postmenopausal, low-trauma fractures. In addition, Caucasian men were addressed. These values allow for comparison between pre and postmenopausal women, and between women and men.

The SoundScan Caucasian population reference values were derived from a widespread clinical program, including both rural and urban populations, and spanning the age range of 20-89. This reference population represents healthy people, with no prior history of low impact fractures, and none of the typical risk factors associated with bone disease. Results were calculated as the mean ±SD for each decade. To establish the validity of the population reference values for use in the U.S.A. and Europe, the Dunnet's method for multiple comparison was used to compare the results to those obtained in two independent clinical trials in the U.S.A. and Germany. For each decade, a one way analysis of variance was performed, with the site as the blocking factor, and tibial SOS as the independent variable. The Caucasian population reference values are presented as a best fit curve using quadratic regression of tibial SOS on age.

The SoundScan Caucasian population reference includes 1207 women and 542 men, aged 20-89. The results were shown to be statistically equivalent to those obtained in two independent clinical trials conducted in the U.S.A. and Germany.

The reference values are similar in key characteristics to BMD references. For women, all three international reference curves demonstrated the characteristic premenopausal peak and postmenopausal decline commonly seen with BMD. Annual rates of postmenopausal tibial SOS decline for American and German women showed no statistically significant difference to those of Israeli Caucasian's (-5.4, -6.4, -5.9 m/sec/year respectively).

American Caucasian male reference values showed no statistically significant differences from those of Israeli Caucasian male values. Males revealed a statistically significant higher peak value than female counterparts, both achieving peak tibial SOS in the fifth decade of life. Significant

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increase in male tibial SOS is noted between the third and fifth decades, followed by a continuously small, but significant, decrease in the sixth to ninth decades, but by almost one quarter the rate of females (average of -7.2 m/sec/year for women versus -1.9 for men).

Quadratic regression was used to produce the final overall Caucasian population reference values incorporated in the SoundScan, as shown in Figure 3.

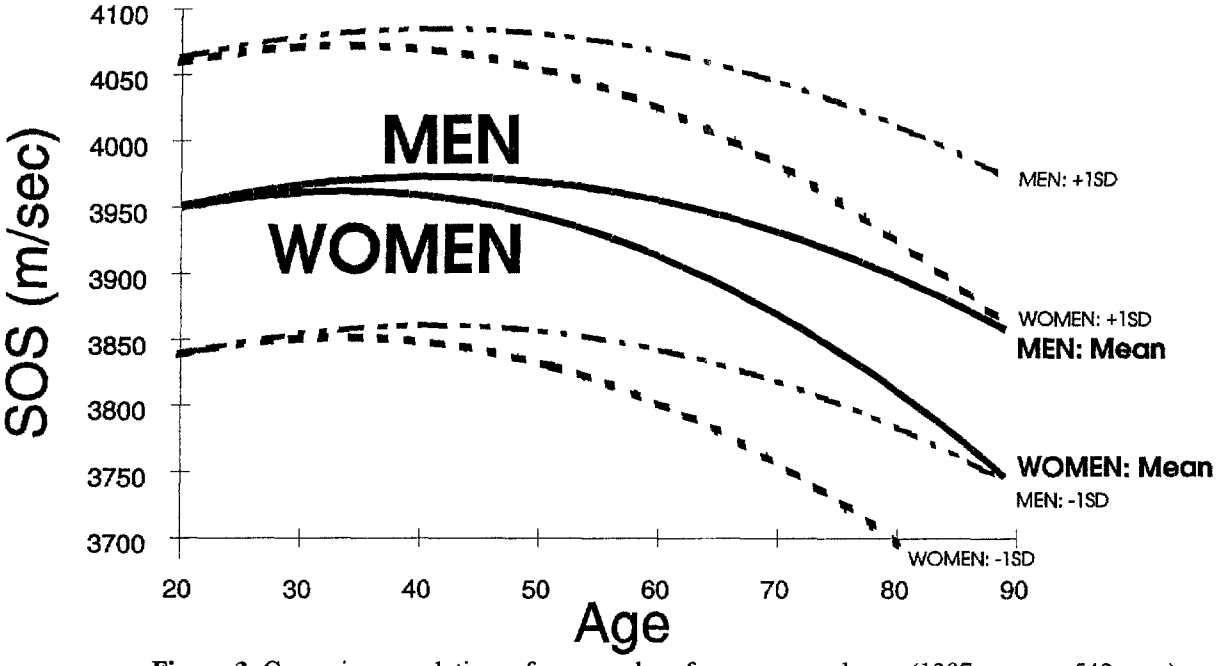

Figure 3: Caucasian population reference values for women and men (1207 women, 542 men) Shown are means and +/-1SD

5. Intertechnology correlations: tibial SOS, and peripheral and axial BMD

The linear relationship between tibial SOS and peripheral and axial BMD was studied by correlation analysis. In addition, intersite BMD correlation was determined, for use as a clinical reference point.

Correlations between technologies were calculated (e.g. between tibial SOS and hip BMD). P-values below 0.05 were considered statistically significant.

Correlation between SoundScan tibial SOS measurements and BMD (hip, forearm, spine) was determined for 858 Caucasian women at five of the clinical centers. Cohort sizes at the participating centers ranged from 72 to 246 women. As shown in Table 6, SoundScan tibial SOS correlates to appendicular and axial BMD measurements in a manner quite similar to the intersite correlations between the various BMD measurements themselves. Shown are the range of correlation results obtained at the various research centers. All results are significant to $p<0.0001$.

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	Hip (neck) BMD	Forearm BMD	Spine BMD
SoundScan tibial SOS	**0.38 to 0.55** n = 72-246	**0.52 to 0.66** n = 97-242	**0.27 to 0.62** n = 97-243
Hip (neck) BMD		**0.45 to 0.58** n = 97-242	
Spine BMD	**0.52 to 0.74** n = 77-243	**0.36 to 0.71** n = 97-239	

Table 6: Intertechnology correlation, Caucasian women

It is noteworthy that at all three centers where tibial SOS was compared with hip, proximal forearm, and spine BMD, the highest correlation was observed between tibial SOS and proximal forearm BMD; both sites are comprised of predominantly cortical bone.

C) ADDITIONAL CLINICAL STUDY: SOUNDSCAN 2000 VERSUS SOUNDSCAN COMPACT

1. The study design

The two SoundScan models were designed to provide equivalent performance. The main hardware, firmware and software components are identical. The clinical measurement and daily phantom verification protocols are identical. The man-machine interface, patient and phantom reports, and population reference values are all identical. To confirm expected equivalence between the two models, a side-by-side validation study was performed at the Chaim Sheba Medical Center, Tel Hashomer, Israel. Specifically, the following performance characteristics were assessed:

a. In-vivo precision

In-vivo precision testing was performed as per the FDA guidance for densitometry device assessment, and is expressed as the coefficient of variation (CV%). The calculation was based on a set of pairs of measurements, one on each SoundScan model, executed on a set of subjects by one operator.

b. Correlation

The linear relationship between the two SoundScan models was studied by correlation analysis. P-values below 0.05 were considered statistically significant.

A pair of tibial SOS measurements were performed on each subject, one measurement with each model. Both measurements were made on the same leg. The study investigators were masked regarding the test subjects.

2. The study population

The study was a non-randomized open study. There were no exclusion criteria. Clinic patients and/or volunteers of both sexes and any age were included, regardless of medical condition. There were 97 women and 2 men who had measurements performed on both SoundScan models, distributed in age from the fourth to the eighth decade, with a representative range of weight and height. This distribution amply represents the desired relevant population for these devices, defined as those women likely to experience postmenopausal, low trauma fractures.

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3. Results

a. In-vivo precision

For the 198 measurements made on the 99 subjects, the in-vivo precision (CV%) was 0.23%, and is within stated product specifications.

b. Correlation

For the 99 subjects, the associated correlation between the two models was 0.995 ($p<0.0001$) as shown in Figure 4.

The data confirms that the two SoundScan models perform in an equivalent manner, as expected, given the common elements of the hardware, firmware, and software design.

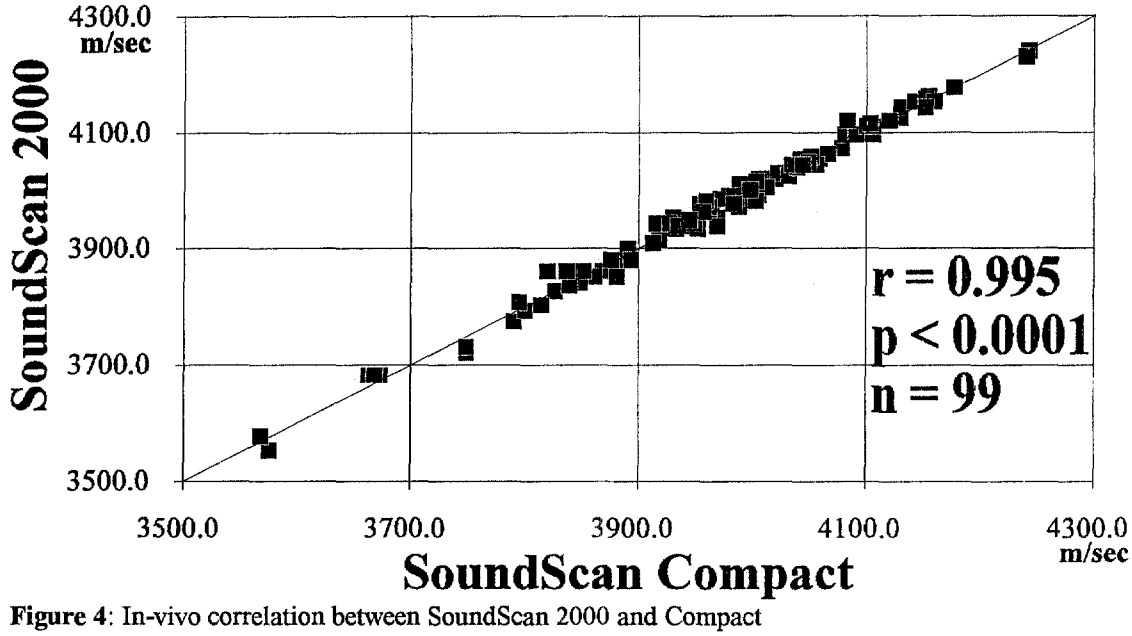

Figure 4: In-vivo correlation between SoundScan 2000 and Compact

XI. CONCLUSIONS DRAWN FROM THE STUDIES

A) RISK/BENEFIT ANALYSIS

The SoundScan is a useful clinical indicator of skeletal status, the clinical effectiveness of which, compares to that of rivals that of established densitometry (BMD), but without exposure to ionizing radiation. Due to the low power levels used, the risks posed by the SoundScan are also significantly lower than the already minimal risks posed by medical ultrasound devices used for other indications (e.g. imaging). Therefore it is reasonable to conclude that the benefits of the SoundScan outweigh the risk of illness or injury when used in accordance with the directions for use.

B) SAFETY

Of the 5,357 people assessed during the clinical evaluation program, there were no reported complications, adverse events or side effects. This clinical experience, combined with the additional clinical experience of SoundScan systems distributed worldwide, demonstrates the safety of the SoundScan.

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C) EFFECTIVENESS

The SoundScan studies show that the devices (1) provide accurate and precise measurements of SOS in the Tibia, (2) provide SOS measurements that behave in a similar manner to other accepted assessments of skeletal status, i.e. peripheral and axial BMD, relative to age, menopause and gender, and (3) can discriminate between patients with and without low trauma fractures in a comparable way to other accepted assessments of skeletal status, i.e. peripheral and axial BMD.

XII. PANEL RECOMMENDATIONS

At a meeting held on November 17, 1997, the Radiological Devices Panel recommended that Myriad Ultrasound Systems' PMA for the SoundScan Bone Sonometer be considered approvable with the condition that the labeling be revised.

XIII. FDA DECISION

CDRH concurred with the Radiological Devices Panel recommendation of November 17, 1997, and issued a letter to Myriad Ultrasound Systems Ltd. on November 26, 1997 advising that its PMA was approvable subject to the submission of 1) revised labeling, 2) a more accurate description of the reference population, and 3) the results of a biocompatibility test for sensitization for natural rubber. In subsequent amendments to the FDA, Myriad Ultrasound Systems adequately addressed the conditions specified by the panel and the FDA. The applicant's manufacturing facility was inspected on March 30, 1998 and was found to be in compliance with the device Good Manufacturing Practice regulations. FDA issued an approval order on May 29, 1998.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Hazards to Health From Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the attached labeling.

XV. REFERENCES

[1] ***Osteoporosis: A guide to diagnosis, prevention, and treatment***, Robert Lindsay, National Osteoporosis Foundation, Raven Press, New York, 1992, Introduction.

[2] ***Noninvasive assessment of bone mineral and structure: State of the art***, H.K. Genant et al., Journal of Bone and Mineral Research, (1996) 11:707-730

[3] ***Appendicular bone density and age predict hip fracture in women***, S.R. Cummings et al., (1990) JAMA 263 (5):665-668

[4] ***Postmenopausal bone loss and the risk of osteoporosis***, C. Christiansen, Osteoporosis International (1994) Suppl 1: S47-51

[5] ***The role of ultrasound In the assessment of osteoporosis: A review***, C.F. Njeh, C.M. Boivin and C.M. Langton. Osteoporosis International (1997) 7:7-22

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[6] ***Perspectives - Ultrasound assessment of bone***, Jonathan Kaufman and Thomas Einhorn, Journal of Bone and Mineral Research (1993) 8(5);514-525

[7] ***Calcaneal ultrasonic measurements discriminates hip fracture independently of bone mass***, C.H. Turner et al., Osteoporosis International (1995) 5:130-135

[8] ***Ultrasonigraphic heel measurements to predict hip fracture in elderly women: The Epidos prospective study***, D. Hans et al., The Lancet (1996) 348: 511-514

[9] ***Ultrasonic velocity measurements through the calcaneus: Which velocity should be measured?***, C.G.Miller, R.J.M.Herd, T.Ramalingam, I.Fogelman, G.M.Blake, Osteoporosis International (1993) 3:31-35.

[10] ***Osteoporosis: association of recent fractures with quantitative US findings***, C.C. Gluer, S.R. Cummings, D.C. Bauer, et al. Radiology Vol. 199:725-32, 1996.

[11] ***Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women***, D.C. Bauer, C.C. Gluer, J.A. Cauley, T.M. Vogt, K.E. Ensrud, H.K. Genant, D.M. Black, Archives of Internal Medicine, Vol. 157:629-633, 1997.

[12] ***Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report,*** J.A.Kanis and the WHO Study Group, Osteoporosis Int. (1994); 4; 368-381.

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2. ESSENTIAL PRESCRIBING INFORMATION (SoundScan Models 2000 & Compact)

Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner)

2.1 Brief Device Description

The SoundScan is a PC-based device which measures the velocity of ultrasound (speed of sound, SOS, in m/sec) along the tibia (tibial SOS), exclusively within bone, unaffected by overlying soft tissue. The device calculates the actual SOS along a defined longitudinal distance in the cortical layer of the tibia. Results are expressed in meters per second (m/sec), and are also presented in units of standard deviations relative to population reference values, e.g., statistical "T" (young-adult) and "Z" (age-matched) scores. Together with the complete history of patient measurements, results are displayed graphically and numerically, both on-screen and in printed reports. The device also includes a detailed patient file with complete biographic information and a profile of risk factors commonly associated with bone disease. Use of this file is at the discretion of the physician, and sections or all of it can be printed out as part of a comprehensive patient report. The patient file also provides automatic follow-up visit scheduling and tracking.

There are two models of the SoundScan, the 2000 and the Compact. The SoundScan 2000 is supplied as a complete mobile workstation, including an integral PC, printer, and console. The SoundScan Compact is a small, light and portable system component, and connects to a personal computer or laptop. The difference between the two models is simply that the PC is integral to the SoundScan 2000, yet external to the SoundScan Compact. Both models are supplied with specialized ultrasound transducer, verification (QC) phantom, Installation Guide, User's Guide and accessories.

SoundScan measurements are made across the tibial plane at the mid-tibia with the patient sitting or lying down. The mid-tibia is defined as the midpoint between the apex of the medial malleolus and the distal apex of the patella, identified by palpation with the patient's leg in the extended position. A complete patient measurement consists of a series of SOS readings (samples) taken as the transducer is moved across the tibial plane, along the mid-tibial circumference. At the conclusion of the 2-3 minute measurement, a single representative result is automatically computed and displayed. Standard commercial ultrasound gel is applied to the region to facilitate acoustic contact.

No instrument calibration is required. Daily system verification is accomplished using the verification (QC) phantom supplied with the device, and the SoundScan provides PASS/FAIL feedback to the operator.

2.2 Intended Use / Indications

The intended use of the SoundScan Bone Sonometer is to perform quantitative ultrasound measurement of the tibia (shin bone), the result of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone strength and, ultimately, in the determination of fracture risk.

The SoundScan measures the velocity of ultrasound (speed of sound, SOS, in m/sec) along the tibia, exclusively within bone, unaffected by overlying soft tissue. SOS along the tibia provides an index of bone strength, with stronger bone having higher velocities. As such the SoundScan provides a measure of skeletal fragility. The SoundScan reports SOS along with both T- and Z-scores.

2.3 Contraindications

None known.

2.4 Warnings

Prior to using the SoundScan, users should read the "Individualization of Treatment" item in this Essential Prescribing Information section in order to properly interpret patient results.

The SoundScan should not be used to assess patients whose skin is abraded and/or have an open sore in the area that comes into contact with the system.

The SoundScan should not be used in the presence of explosive agents.

2.5 Precautions

Do not expose this instrument to rain or moisture.

For the SoundScan Compact, interfacing equipment (computer, monitor, printer) must meet IEC 601, or IEC 950 or equivalent safety standards, depending upon installation configuration. Refer to the SoundScan Installation Guide supplied with your system.

2.6 Adverse Events

No adverse events were reported in the course of the clinical studies performed, in which a total of 5,357 subjects underwent SoundScan examinations. There are no known potential adverse effects of the SoundScan Bone Sonometer on health.

2.7 Clinical Studies

Studies at six international clinical research centers in the U.S.A., Israel, United Kingdom, and Germany were conducted to determine if the SoundScan measurement of tibial speed of sound (tibial SOS):

1. is a precise (reproducible) measurement.

2. provides results similar to other accepted assessments of skeletal status, i.e. peripheral and axial BMD, relative to age, menopause, and gender.

3. can discriminate between patients with and without low trauma fractures as effectively as other accepted assessments of skeletal status, i.e. peripheral and axial BMD.

5,357 Caucasian women and men were studied using cross-sectional protocols, and the studies were effectively blinded. Basic demographic data is shown in Table 2-1.

	Total #people studied	#Women	#Men	Overall age range
U.S.A.	381	195	186	30-96
U.S.A.	97	97	0	61-80
U.K.	688	681	7	15-98
Germany	198	193	5	21-97
Israel	256	251	5	24-87
Israel	3737	3023	714	15-98
Totals	**5357**	**4440**	**917**	

Table 2-1: Study populations

The subjects spanned a wide age range, with special emphasis on the peri and postmenopausal ages, those ages most associated with low-trauma fractures. The population distribution by decade of age is shown in Table 2-2.

10-19	**7**
20-29	**238**
30-39	**468**
40-49	**836**
50-59	**948**
60-69	**1082**
70-79	**1136**
80-89	**610**
90-99	**32**
Total	**5357**

Table 2-2: Distribution by decade of age

The objective of the clinical studies was to verify expected performance trends of tibial SOS, and to compare its performance with peripheral and axial bone densitometry. Specifically, the following five key performance characteristics were assessed:

1. In-vivo precision was assessed by repeat measurements on subjects.

2. The relationship of tibial SOS to anthropometric parameters, and comparison to peripheral and axial BMD, was assessed by correlation analysis.

3. The intertechnology correlations between tibial SOS and peripheral and axial BMD were assessed by correlation analysis.

4. The discriminatory ability of tibial SOS for postmenopausal women with appendicular and vertebral low trauma fractures, and comparison to peripheral and axial BMD, was assessed by standard statistical methods (t-tests, sensitivity/specificity, ROC, odds ratios). Comparison was made to both premenopausal and age-matched, non-fracture controls.

5. Population reference values were compiled for Caucasian women and men. This reference population represents healthy people, with no prior history of low impact fractures, and none of the typical risk factors associated with bone disease.

The following summarizes the results:

In-vivo precision

In-vivo precision of the SoundScan was calculated as the coefficient of variation based on repeated measurements on a set of individuals. Precision was determined in groups of 10 to 97 subjects at five of the clinical centers. A total of 492 measurements were performed on 192 subjects, ranging in age from 22-80, and including healthy people, bone clinic patients, and patients with diagnosed osteoporosis. Results are summarized in Table 2-3, as compared to published results for axial and peripheral BMD CV%. Also shown is standardized precision (SCV), a method for standardizing and comparing precision across different technologies, and provided for gross comparison between tibial SOS and appendicular and axial BMD.

	SoundScan tibial SOS	BMD (Spine, hip, forearm)
Mean CV%	**0.37%**	1.0 - 3.0%*1
Standardized CV%*2	**3.1%**	1.5 - 5.2%

Table 2-3: In-vivo precision

*1 CV% for BMD is cited from ***Noninvasive Assessment of Bone Mineral and Structure: State of the Art***, Journal of Bone and Mineral Research (JBMR), 1996, H.Genant et al., Vol. 11 (6) 707-730 [2]

*2 Standardized CV% is defined in Miller et al. [9]. Standardized CV% was calculated for both the SoundScan and BMD, using the CV% cited above and population means and ranges derived from the data of 97 to 3023 women across the various centers

Correlation to anthropometric parameters

The correlation of SoundScan tibial SOS measurements with anthropometric parameters, i.e., age, years since menopause, height, weight, and BMI was determined for women at five clinical centers. Concurrent axial and peripheral BMD measurements were obtained where possible. Tibial SOS behaved similarly to BMD relative to anthropometric parameters, insofar as it exhibited expected reduction relative to age and menopause.

Linear trends of SoundScan tibial SOS versus age for Caucasian pre- and postmenopausal women are shown in Figure 2-1 for each of five of the clinical centers. SoundScan tibial SOS exhibits a statistically insignificant change in premenopausal adulthood, followed by a significant decrease in the postmenopausal years.

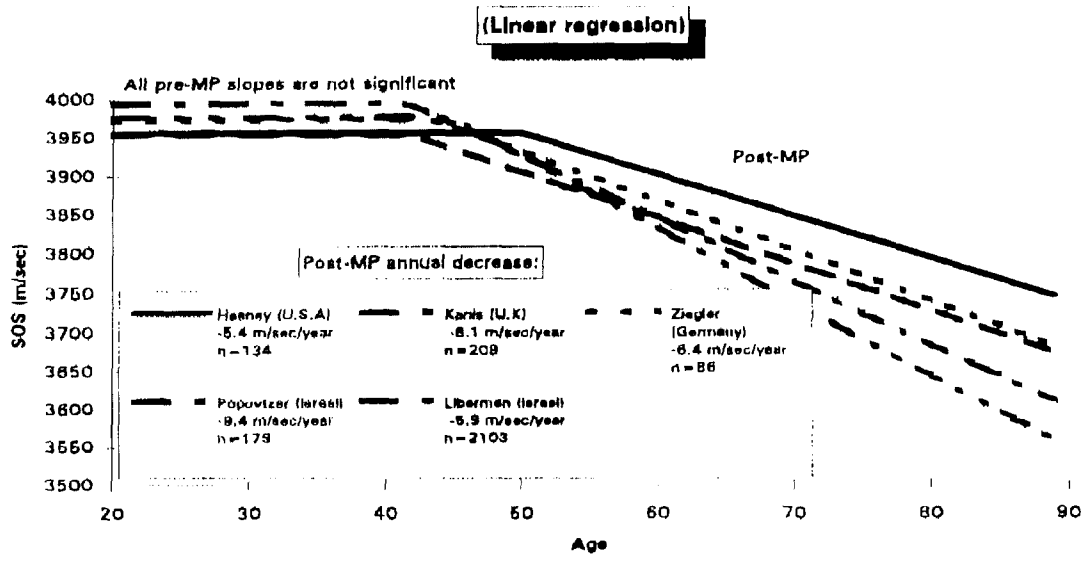


Figure 2-1: Tibial SOS versus age for Caucasian pre- and post-MP women

For the two clinical centers studying both women and men, tibial SOS declines 2.5 to 3.4 times as fast per annum in Caucasian women than in men.

Discriminatory ability for low trauma postmenopausal fracture

Discriminatory ability was defined as the ability of the SoundScan to discriminate between postmenopausal women (Post-MP) with low trauma fractures and two groups: premenopausal (Pre-MP) and postmenopausal non-fracture controls. This was studied in a total of 2057 women at six centers, including 1201 postmenopausal age-matched comparisons, as shown in Table 2-4. Totals at the individual centers ranged from 63 to 1206 women each.

Pre-MP non-fracture	856
Post-MP non-fracture	814
Post-MP fracture (162 appendicular fx, 225 vertebral fx)	387
Total	2057

Table 2-4: Discriminatory analysis: # women

SoundScan tibial SOS demonstrated significant discriminatory ability, similar to BMD, for postmenopausal low trauma appendicular and vertebral fractures versus premenopausal non-fracture controls (5 centers). Sensitivities of tibial SOS (at T=-1SD) ranged from 83% to 100% for appendicular fracture and 64% to 93% for vertebral fracture. Associated specificities ranged from 84% to 89% for both types of fractures. Hip, forearm, and spine BMD results were similar. To lend clinical perspective, mean T-scores were calculated for the fracture cohort relative to the individual center's non-fracture control group. Results are shown in Table 2-5.

Fracture type	**#centers**	**n, total**	**Mean T-score (Range)**
Appendicular fracture	3	162 fx, 758 non-fx	**-3.4** (-2.3 - -4.6)
Vertebral fracture	4	121 fx, 815 non-fx	**-2.4** (-1.6 - -3.1)
Overall average, both types	5	283 fx, 856 non-fx	**-2.8**

Table 2-5: Mean T-scores for fracture cohorts

SoundScan tibial SOS demonstrated significant discriminatory ability for appendicular, low trauma fractures versus age-matched, non-fracture controls, as determined by t-tests for differences between the means (3 centers).

Three centers reported significant discriminatory ability of SoundScan tibial SOS for postmenopausal low trauma, vertebral fractures versus age-matched, non-fracture controls as determined by t-tests for differences between the means. Two centers found non-significant discrimination. In the latter two studies, hip and forearm BMD also did not reveal any significant difference between the fracture and non-fracture cohorts. Associated odds ratios ranged from non-significant to 2.5, and behaved similarly for hip, forearm, and spine BMD.

Receiver operating characteristic (ROC) curve analysis revealed areas under the curves (AUC) as shown in Table 2-6. Results whose p-value ≥ 0.05 have an area which is not significantly different from 50%, and are listed as NS.

Populations compared	Range of ROC AUC results for various diagnostic modalities			
	SoundScan tibial SOS	**Hip BMD**	**Forearm BMD**	**Spine BMD**
Post-MP appendicular fx versus pre-MP non-fx	93%-98%	Not studied	93%	Not studied
Post-MP vertebral fx versus pre-MP non-fx	84%-95%	84%-94%	84%-90%	93%
Post-MP appendicular fx versus age-matched non-fx	NS-78%	Not studied	NS	Not studied
Post-MP vertebral fx versus age-matched non-fx	NS-75%	NS-66%	NS-69%	NS-71%

Table 2-6: Areas under the ROC curves

SoundScan tibial SOS Caucasian population reference values

The SoundScan Caucasian population reference includes 1207 women and 542 men, aged 20-89. The results were shown to be statistically equivalent to those obtained in two independent clinical trials conducted in the U.S.A. and Germany

The reference values are similar in key characteristics to BMD references. For women, all three international reference curves demonstrated the characteristic premenopausal peak and postmenopausal decline commonly seen with BMD. Annual rates of postmenopausal tibial SOS decline for American and German women showed no statistically significant difference to those of Israeli Caucasian's (-5.4, -6.4, -5.9 m/sec/year respectively).

American Caucasian male reference values showed no statistically significant differences from those of Israeli Caucasian male values. Males revealed a statistically significant higher peak value than female counterparts, both achieving peak tibial SOS in the fifth decade of life. Significant increase in male tibial SOS is noted between the third and fifth decades, followed by a continuously small, but significant, decrease in the sixth to ninth decades, but by almost one quarter the rate of females (average of -7.2 m/sec/year for women versus -1.9 for men).

Quadratic regression was used to produce the final overall Caucasian population reference values incorporated in the SoundScan, as shown in Figure 2-2.

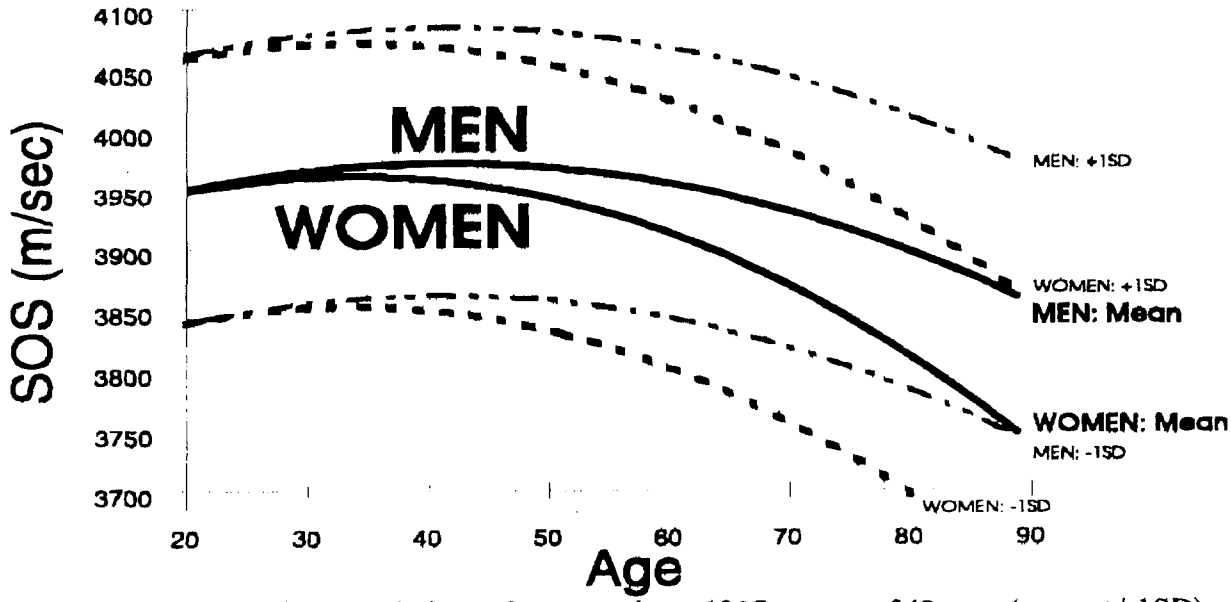


Figure 2-2: Caucasian population reference values: 1207 women, 542 men (mean +/-1SD)

Intertechnology correlation

Correlation between SoundScan tibial SOS measurements and BMD (hip, forearm, spine) was determined for 858 Caucasian women at five of the clinical centers. Cohort sizes at the participating centers ranged from 72 to 246 women. As shown in Table 2-7, SoundScan tibial SOS correlates to appendicular and axial BMD measurements in a manner quite similar to the intersite correlations between the various BMD measurements themselves. Shown are the range of correlation results obtained at the various research centers. All results are significant to $p<0.0001$.

	Hip (neck) BMD	**Forearm BMD**	**Spine BMD**
SoundScan tibial SOS	**0.38 to 0.55** n = 72-246	**0.52 to 0.66** n = 97-242	**0.27 to 0.62** n = 97-243
Hip (neck) BMD		**0.45 to 0.58** n = 97-242	
Spine BMD	**0.52 to 0.74** n = 77-243	**0.36 to 0.71** n = 97-239	

Table 2-7: Intertechnology correlation, Caucasian women

It is noteworthy that at all three centers where tibial SOS was compared with hip, proximal forearm, and spine BMD, the highest correlation was observed between tibial SOS and proximal forearm BMD; both sites are comprised of predominantly cortical bone.

2.8 Individualization of Treatment

What follows is information intended to introduce the physician to the SoundScan measurement, its clinical interpretation, and its relationship to accepted densitometry methods.

2.8.1 Understanding SoundScan measurements: SOS, T- and Z-scores

Introduction

When a patient measurement is completed, there are three ways to assess the single representative speed of sound (SOS) result:

1. To evaluate the result on an absolute scale.

2. To compare the result to those of young, healthy people (T-score).

3. To compare the result to those of people of the same age and sex (Z-score).

For "1", the SoundScan provides the patient's SOS result in m/sec. For "2" and "3", the SoundScan provides the information in the form of T- and Z-scores.

T- and Z-scores provide additional information for the assessment of bone because they take into account both the mean and statistical distribution of population reference values. This can be more important than the absolute result itself.

Young adult comparison: T-score

This comparison compares the patient's result to the peak population mean for young healthy adults, where the peak mean is as shown below in Figure 2-3 for typical population reference values:

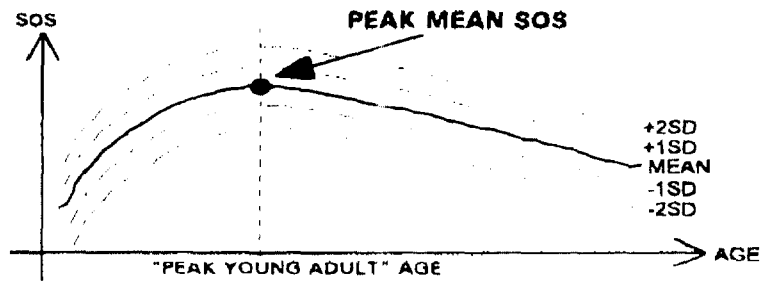


Figure 2-3: Definition of young adult SOS for T-score calculation

The T-score compares the patient's result to the peak population mean and calculates the number of standard deviations above or below the mean that it falls. The formula is as follows:

$$T = \frac{\text{(Patient's result, m/sec - Peak population mean)}}{\text{(Standard deviation of the population reference at the peak age)}}$$

For example, consider an 80 year old woman whose SOS is 3670 m/sec. Suppose that the peak population mean is 3958 m/sec at age 32, and that the standard deviation at this age is 100 m/sec. This woman's T-score is then calculated as follows:

$$T = \frac{(3670 - 3958 \text{ m/sec})}{100 \text{ m/sec}} \Longrightarrow -2.9$$

Many physicians today view the T-score as an indication of skeletal strength because it provides a comparison of the patient's status today relative to the range of healthy young adults.

Age-matched comparison: Z-Score

This comparison compares the patient's result to those of people of the same age and sex, where the mean age-matched value is as shown below in Figure 2-4 for typical population reference values:

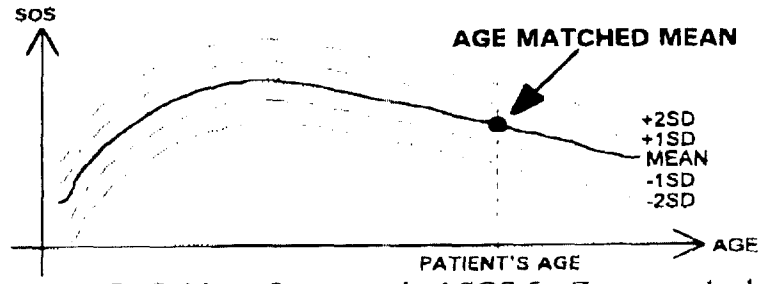


Figure 2-4: Definition of age-matched SOS for Z-score calculation

The Z-score compares the patient's result to the population mean for his/her age and calculates the number of standard deviations above or below it. The formula is as follows:

$$Z = \frac{\text{(Patient's result, m/sec - Population mean at this age, m/sec)}}{\text{(Standard deviation of the population reference at patient's age)}}$$

The standard deviation at a given age may differ from that of "young adult". Therefore, when calculating the Z-score, the standard deviation value used must be matched to the patient's age.

For example, consider the 80 year old woman whose SOS is 3670 m/sec. Suppose that the population mean for 80 year old women is 3784, with a standard deviation at this age of 110 m/sec. This woman's Z-score is then calculated as follows:

$$Z = \frac{(3670 - 3784 \text{ m/sec})}{110 \text{ m/sec}} \Longrightarrow -1.0$$

The clinical significance of this result is that this patient falls within one standard deviation of women her own age, i.e. has a result similar to 70% of her peers. This result indicates that the woman's skeletal status compared to her age-matched peers is reasonable (unless she has either a history of previous measurements that reveal a steeper-than-average downward trend in SOS over time, or other mitigating factors in her patient file that require attention).

Note that in this example, the woman's T- and Z-scores (-2.9 and -1.0 respectively) might lead to different courses of action on the part of the physician. The T-score indicates weaker skeletal strength, whereas the Z-score suggests that the woman is reasonably similar to her peers.

These two ways of interpreting the measurement result, together with the patient's clinical profile, supply the clinician with useful data on which to base diagnostic or therapeutic decisions.

Absolute SOS and T- and Z-scores are all shown on the SoundScan patient report. Shown in the following Figures 2-5 and 2-6 is a description of the SoundScan "Basic" Patient Report (a one-page document), and its interpretation.

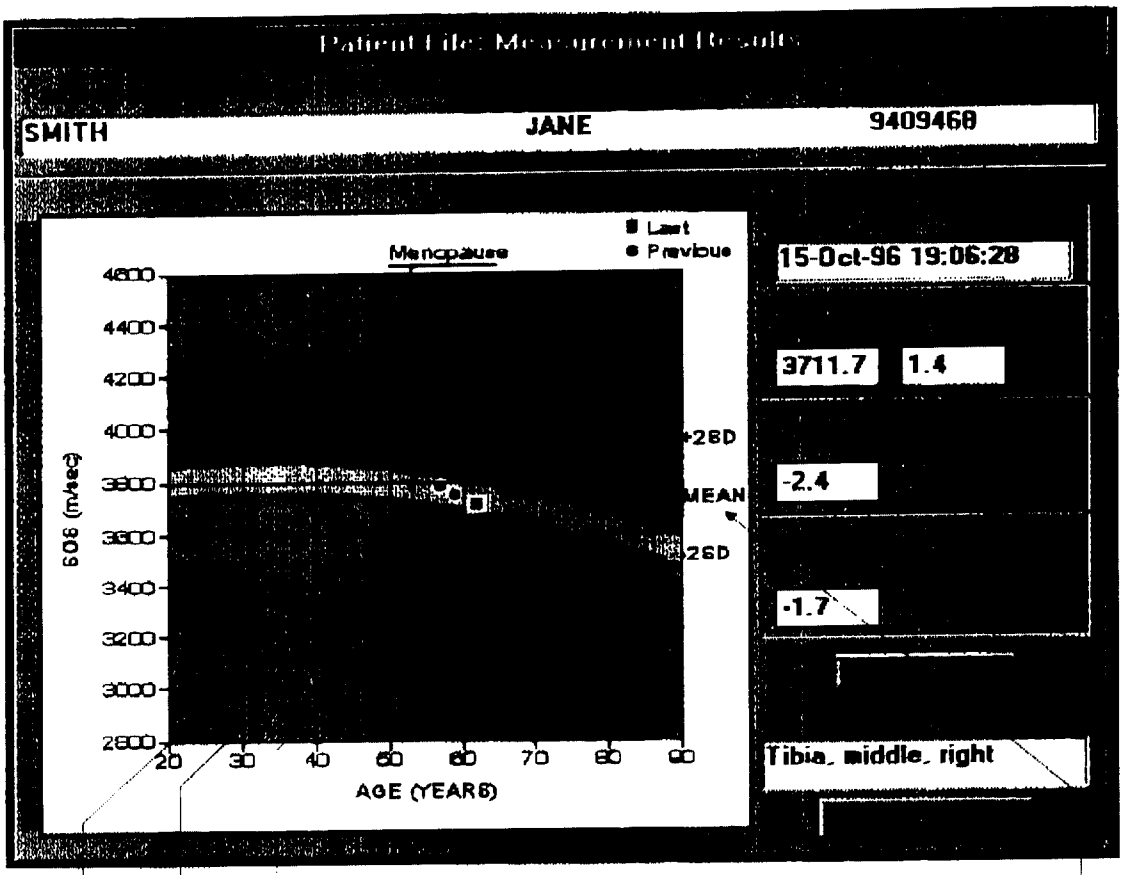
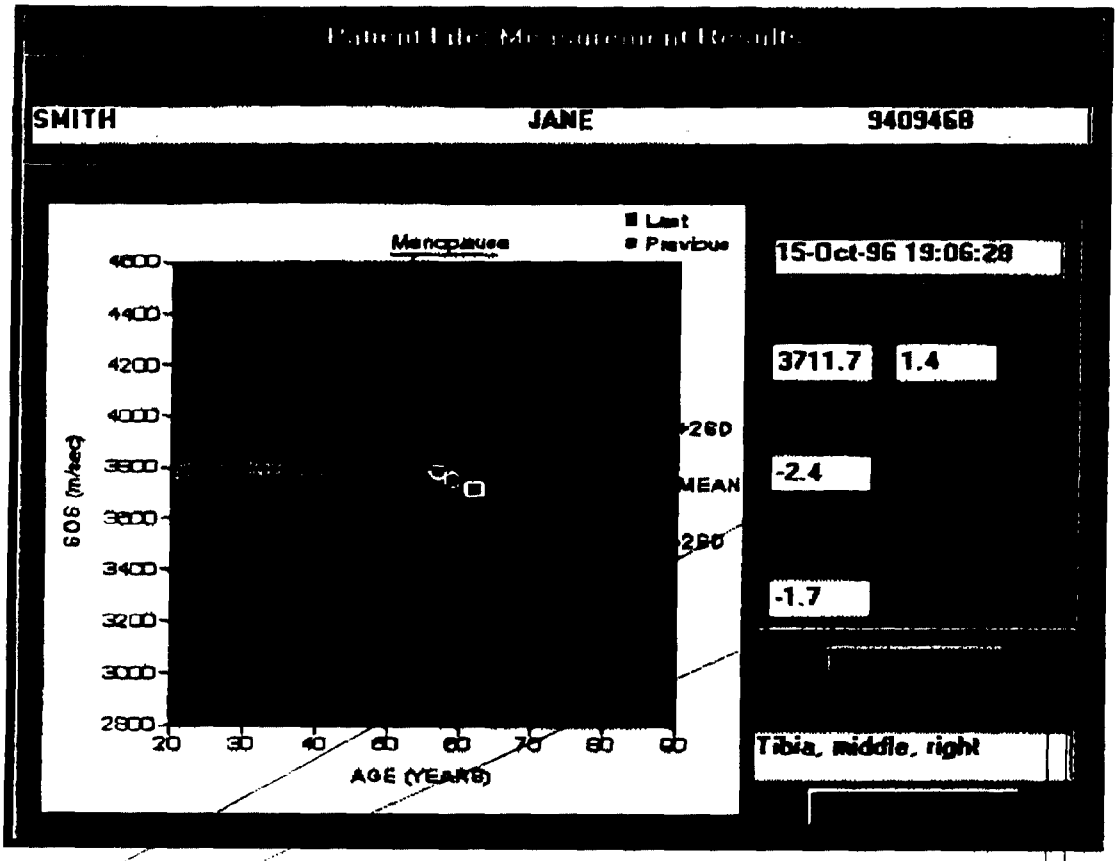


Figure 2-5: SoundScan basic patient report (Detail 1 of 2)



The SPEED OF SOUND (SOS) shown is the final representative result for the measurement.

The SD shown is the standard deviation for the measurement result, and should be viewed as the quality factor for the measurement. An SD of 5 or less indicates a quality measurement.

AGE MATCHED compares the patient's result to the population mean for his/her age. The "Z" score equals the number of standard deviations difference between the patient's score and the population mean for his/her age-matched group.

YOUNG ADULT compares the patient's result to the population mean for young healthy people of the same sex. The "T" score equals the number of standard deviations difference between the patient's score and the population mean for young adults.

Figure 2-6: SoundScan basic patient report (Detail 2 of 2)

2.8.2 The relationship between tibial SOS and peripheral and axial BMD

Introduction

We are often asked about the relationship between the SoundScan's tibial SOS measurement and BMD results. It is quite common to find new SoundScan users comparing the T- and Z-scores from tibial SOS to BMD measurements for an individual patient, expecting to find a perfect match between the two. This section is meant to inform and educate physicians about the use of tibial SOS, and its relationship to BMD.

A perspective on BMD

It is often assumed that two-dimensional BMD measurements represent the true skeletal condition. This can be misleading. While BMD measurements provide one important risk factor for skeletal fragility, it is not the only one. Tibial SOS provides similar, but not identical information about skeletal strength. Thus both technologies play an important role for the clinician.

Within a typical clinical practice, for a given set of patients, BMD will identify certain individuals as having weaker skeletons. For this same set of patients, tibial SOS will identify a similar amount of patients as having weaker skeletons. Most (50-80%) of those patients identified will be common to both technologies. Regarding the remaining people, tibial SOS will identify some individuals with weaker skeletons that BMD will not, and vice versa. This discrepancy is inherent in the unique character of each measurement. There is no single correct answer; each measurement technique provides a risk factor, one piece of the complex puzzle that is overall skeletal fragility and fracture risk.

Intertechnology correlations

BMD is a well-established modality for bone assessment [1-12], and it is industry standard practice to compare all new technologies to BMD. While strong correlation to BMD implies a device which measures similar or identical parameters, moderate correlation implies a device that measures parameters other than, or in addition to BMD. Quantitative ultrasound reflects mechanical properties of bone not measured by BMD.

Correlation between tibial SOS and BMD is similar to the intersite correlations of the BMD measurements themselves. Hip, forearm, and spine BMD correlate with each other in the range of 0.4 to 0.7. Each individual site has proven itself to be of clinical value for the diagnosis of osteoporosis, yet each site does not definitively predict the results at the other sites. Similarly, tibial SOS correlates to BMD within this same range of 0.4 to 0.7. It too has proven itself to be of clinical value for the diagnosis of osteoporosis; and it too does not definitively predict the results at the other sites.

Correlation data by itself is not the best measure of a technology's value. Regardless of the results, it is the in-vivo discriminatory ability of a device to distinguish between fracture and non-fracture patients, between strong and weak skeletons, which truly defines a technology's clinical value.

Discriminatory ability: The key performance parameter

For the diagnosis of disease, the discriminatory ability of the device is the most important performance characteristic. For osteoporosis, statistically significant differences between postmenopausal women with low trauma fracture versus non-fracture controls, especially for age-matched comparisons, provides vital confirmation for a given technology. For both tibial SOS and peripheral and axial BMD, discriminatory results are similar.

T- and Z- scores provide a common language for tibial SOS and BMD measurements, and the T-score is the basis for classification of patients as either osteoporotic or osteopenic. According to the WHO criteria, osteoporosis is defined as any individual whose BMD T-score is -2.5 or lower as compared to young healthy controls [12]. Worldwide clinical data document that tibial SOS discriminates between people with and without fractures according to the same WHO criteria. Overall, for people with appendicular and vertebral fractures, mean T-score values for tibial SOS are -2.8 standard deviations (SD).

2.9 Patient Counseling Information

An "Information for Patients" handout is included in Chapter 4 (PATIENT'S MANUAL) of this SoundScan User's Guide. It provides a brief introduction to osteoporosis, osteoporosis diagnosis, ultrasound bone sonometry, and the SoundScan Bone Sonometer measurement.

2.10 Conformance to Standards

The SoundScan conforms to international standards for safety and electromagnetic compatibility. In fact, this device uses ultrasound power levels lower than standard imaging ultrasound devices which are widely used and accepted. Refer to Appendices C and F in Chapter 3.

2.11 How Supplied

The SoundScan 2000 is supplied as a complete mobile workstation, including an integral PC, printer, and console. The SoundScan Compact is a small, light and portable system component, and connects to a personal computer or laptop (The computer must meet the minimum PC/laptop hardware requirements specified in the SPECIFICATIONS section of this SoundScan User's Guide). The difference between the two models is simply that the PC is integral to the SoundScan 2000, yet external to the SoundScan Compact. Both models plug into a standard power outlet. Both models use the same ultrasound transducer and daily verification (QC) phantom, and share the same clinical measurement protocol, machine-user interface, population reference values, and patient report format.

Peripheral equipment for the SoundScan 2000 includes monitor, keyboard, mouse, printer, mobile console, and a footswitch for hands-free on/off control of the measurement. Peripheral equipment for the SoundScan Compact includes a communication adaptor for connection to the computer and printer, and a footswitch.

The SoundScan is supplied with both an Installation Guide and a complete User's Guide which includes physician and patient educational material, and the SoundScan Patient Questionnaire, a data collection form which mimics the system's patient file. Accessories include a tape measure and skin marker for determining the measurement site, and commercially available ultrasound gel.

2.12 Operator's Manual

Attached.

2.13 Patient's Manual

An "Information for Patients" handout is included in Chapter 4 (PATIENT'S MANUAL) of this SoundScan User's Guide. It provides a brief introduction to osteoporosis, osteoporosis diagnosis, ultrasound bone sonometry, and the SoundScan Bone Sonometer measurement.

2.14 References

[1] ***Osteoporosis: A guide to diagnosis, prevention, and treatment***, Robert Lindsay, National Osteoporosis Foundation, Raven Press, New York, 1992, Introduction.

[2] ***Noninvasive assessment of bone mineral and structure: State of the art***, H.K. Genant et al., Journal of Bone and Mineral Research, (1996) 11:707-730

[3] ***Appendicular bone density and age predict hip fracture in women***, S.R. Cummings et al., (1990) JAMA 263 (5):665-668

[4] ***Postmenopausal bone loss and the risk of osteoporosis***, C. Christiansen, Osteoporosis International (1994) Suppl 1: S47-51

[5] ***The role of ultrasound in the assessment of osteoporosis: A review***, C.F. Njeh, C.M. Boivin and C.M. Langton. Osteoporosis International (1997) 7:7-22

[6] ***Perspectives - Ultrasound assessment of bone***, Jonathan Kaufman and Thomas Einhorn, Journal of Bone and Mineral Research (1993) 8(5);514-525

[7] ***Calcaneal ultrasonic measurements discriminates hip fracture independently of bone mass***, C.H. Turner et al., Osteoporosis International (1995) 5:130-135

[8] ***Ultrasonigraphic heel measurements to predict hip fracture in elderly women: The Epidos prospective study***, D. Hans et al., The Lancet (1996) 348: 511-514

[9] ***Ultrasonic velocity measurements through the calcaneus: Which velocity should be measured?***, C.G.Miller, R.J.M.Herd, T.Ramalingam, I.Fogelman, G.M.Blake, Osteoporosis International (1993) 3:31-35.

[10] ***Osteoporosis: Association of recent fractures with quantitative US findings***, C.C. Gluer, S.R. Cummings, D.C. Bauer, et al. Radiology Vol. 199:725-32, 1996.

[11] ***Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women***, D.C. Bauer, C.C. Gluer, J.A. Cauley, T.M. Vogt, K.E. Ensrud, H.K. Genant, D.M. Black, Archives of Internal Medicine, Vol. 157:629-633, 1997.

[12] ***Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report***, J.A.Kanis and the WHO Study Group, Osteoporosis Int. (1994); 4; 368-381.

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INFORMATION FOR PATIENTS: OSTEOPOROSIS, BONE ASSESSMENT, AND YOU

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#pages:	4

What you should know about osteoporosis

Osteoporosis is a condition which thins and weakens your bones, making you more likely to break (fracture) bones, even from minor knocks, bangs, or falls. People with osteoporosis most commonly experience fractures of the spine, hip or wrist.

There are approximately 25 million Americans affected by this "silent" disease, and most of them are not even aware of the condition until a fracture occurs. Although osteoporosis is a significant health problem for many Americans, it is most common in middle-aged women. As many as one in two women and one in five men, over age 50, will suffer a fracture related to osteoporosis during their lifetime.

What causes osteoporosis?

Your bones are made of living tissue. Although you are not aware of this, your bones are always changing. They are being both eroded and rebuilt in two, on-going activities which together are called "remodeling".

In your teens and twenties, the "rebuilding" dominates, and your bones get stronger and stronger. In your thirties and forties, the two activities more or less balance each other out, and your bones reach their peak strength. Peak bone strength depends on many factors, including genetics, lifestyle (diet and exercise), medication and chronic illness. After the age of forty, the "eroding" becomes dominant, and over time your bones gradually weaken.

Normally, there is no cause for concern - remodeling is part of the natural life cycle for us all. However, if you develop osteoporosis, "rebuilding" slows down earlier, or "eroding" speeds up, or both. With osteoporosis, the net result is that your bones become weaker than those of other people your own age, and you have a greater tendency to fracture.

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Who is prone to osteoporosis?

If you are a postmenopausal woman, you are in the group who will most likely be affected by osteoporosis. With the onset of menopause, your body slows its production of the important hormone, estrogen. This hormone was important during your reproductive years, and also helped to keep your bones strong.

There are other risk factors which may lead to osteoporosis. These include a family history of osteoporosis, a small, light body frame, smoking and alcohol consumption, a lack of exercise, and long-term use of certain drugs such as corticosteroids, and early menopause.

How do you check if you are at risk for osteoporosis?

The best place to start is with your doctor. He or she will review your entire medical history, and if there is concern for osteoporosis, he/she may advise you to have a bone check-up. The results of this test, combined with your medical history, will help your doctor decide if you have, or might develop, osteoporosis.

What kind of bone check-ups are there?

Until the 1970's and 1980's, the best way to check your bones was to x-ray your hip or spine. An experienced radiologist could see from the x-ray if your bones were in trouble. But weak bones are only visible once they are significantly damaged and have already partially collapsed. So this test was ineffective as an "early warning system", and it was unwise to expose people to unnecessary radiation. Therefore, clinicians and engineers worked together to develop better, safer methods for earlier bone testing.

In the 1970's and 1980's, special radiological tests were developed to help detect osteoporosis earlier. These tests are called Bone Mineral Density (BMD) tests. BMD has been the most popular method for checking bone. Its measurements tell the doctor how much bone there is at a particular site on your body, referred to as your bone density. The lower the density, the weaker your bone, and the more prone you are to fracture. The measurement can be performed at various sites such as the spine, hip, arms and legs. BMD measurements also involve radiation, although at a much lower level than traditional x-rays.

In 1997, a new technology was approved by the U.S. Food and Drug Administration for testing your bones. This new method, called "Bone Sonometry", is based on ultrasound, similar to the ultrasound that doctors use to check pregnant women and their unborn babies. If you are reading this pamphlet, it is likely that your doctor has chosen to test your bones with this new generation of equipment, called "Bone Sonometers".

BMD and Bone Sonometry are not always used on the same sites of the body, and results of the tests are not always the same. Each technology measures somewhat different things, at different places. Nevertheless, since osteoporosis is a generalized disease, affecting your entire skeleton, it can be detected at various body sites. Your doctor understands this, and knows how to interpret the results so that the two of you can make more informed decisions about your health.

Why use ultrasound to check bones?

Ultrasound has a long and successful history, dating back to the early 1900's. It has been widely used in industry to detect defects or flaws in materials - for example, cracks in airplane wings and pipelines. Bone sonometry uses similar principles to provide information about your bones. The ultrasound waves pick up important information about your bones' density, elasticity, and thickness. Today's ultrasound bone sonometers measure at the arm or leg. It's fast, comfortable, dependable, and most importantly, radiation free.

How is an ultrasound bone check-up done?

You will either sit in a chair or lie on your back on an examination table, with one leg outstretched. The length of your tibia (shin bone) will be measured, and a line will be marked on the skin at the middle, using a skin marker. Standard ultrasonic gel will be applied to the skin, and the operator will move the scanner back and forth along the midline. This may be repeated on your other leg, too.

What should you wear?

You only need to expose your leg, from the knee down. It is best that you wear loose fitting pants or a skirt. If you wear pantyhose, you'll need to remove them.

How long does this check-up take?

The whole test only takes about 3-4 minutes.

Are there any risks involved in ultrasound bone testing?

No, ultrasonic waves used in medical applications do not present any known risk or side effects.

Test results and their meaning

Your ultrasound bone check-up provides three important pieces of information:

1. The first is the actual score of your test (it's actually a measurement of how fast ultrasound waves travel through your bone, called "Speed Of Sound", or "SOS" - for example, 3850 meters per second).

2. Next, your results are compared with those of typical young, healthy people of your sex, and summarized in a number called a "T-score".

3. Finally, your results are compared with those of people your own age and sex, and summarized in the third and final number, the "Z-score".

All this information is then printed out, along with the results of previous check-ups you've had at the same center. By the way, the meaning and significance of the "T" and "Z" scores for both ultrasound and BMD are very similar. Because of this, most doctors will understand both types of results.

Having a low result does not mean that you will definitely fracture your bones in the future. Your doctor knows how to interpret the numbers, and can discuss with you what these results mean.

What should you do with the results?

Your doctor will advise you as to what is best to do. If your test results indicate that your bones may be weak, he/she will probably suggest preventive measures and/or prescribe medications. How your doctor helps you care for yourself depends upon many factors. In any event, you can help your bones by....

- ✓ ...eating healthy foods.
- ✓ ...making sure your diet includes enough calcium (very important for building strong bone - for example, dairy products, fish with bones like sardines).
- ✓ ...doing weight-bearing exercise (where your body supports its own weight, like walking, jogging, aerobics. Swimming is a great exercise for your heart and easy on your joints, but it's not the best choice for strengthening your bones).
- ✖ ... avoiding heavy smoking and alcohol consumption.